Thorax, 1978, **33**, 629–634

Pulmonary haemodynamics and function immediately after canine left lower lobe preservation[1]

JOSHUA A BARDIN, PETER M TAFT, AND NICHOLAS A HALASZ

From the Department of Surgery, University Hospital, University of California Medical Center, San Diego, California 92103, USA

Bardin, J A, Taft, P M, and Halasz, N A (1978). *Thorax*, **33**, 629–634. **Pulmonary haemodynamics and function immediately after canine left lower lobe preservation.** After temporary reimplantation of the left lower lobe in dogs, the effects of various preservation techniques on the canine lung were assessed. Vascular resistance, shunt fraction, weight gain, and airway pressure were found to reflect and predict the effectiveness of various preservation techniques compared with reported survival data.

Most studies dealing with experimental lung preservation have measured success in terms of survival and long-term pulmonary function. In a previous study we described a model for determining the effects of preservation on pulmonary haemodynamics and gas exchange immediately after reimplantation and found that three hours of warm preservation in the atelectatic state leads to appreciable changes in blood flow, vascular resistance, lung weight, and shunt fraction during the hour after preservation (Taft *et al*, 1976). The experiments to be described deal with the effects of atelectasis, inflation, ventilation, and flushing with Collins solution on warm and cold preserved lobes.

Methods

The surgical procedure used has been described in detail by Taft *et al* (1976). Briefly, mongrel dogs weighing 18–24 kg were anaesthetised, intubated, and ventilated with tidal volumes, respiratory rates, and dead space calculated (and adjusted) to maintain a normal pH and blood gases. The chest was entered through the fifth left intercostal space, the left upper and middle lobes were excised, and the left lower lobe (LLL) was removed, weighed, and either reimplanted immediately or preserved by one of the methods described below. Before reimplantation a Statham-Gould flow probe was applied to the main pulmonary artery (MPA), and a Swan-Ganz catheter was passed into a distal right pulmonary artery (PRA).

[1]Supported by National Institutes of Health Grant PHSHL 17944.

Reimplantation was accomplished by reconnecting the severed artery over the largest cannulating Statham-Gould flow probe that the artery would accept. The left pulmonary vein (LPV) was cannulated with a T-connector that was inserted through a purse-string into the left atrial appendage. The side arm of this connector was used to measure left atrial (LA) pressure and to obtain LLL venous effluent blood. The left main bronchus was cannulated and ventilated with a tidal volume and dead space calculated to deliver 27% of total ventilation to the LLL. The animals were ventilated with room air except during shunt studies when 100% oxygen was used. Airway pressure was measured by water manometers connected through side arms to the air hoses supplying the right lung and LLL. An end-expiratory pressure of 5 cm of water was maintained during the experiments.

MEASUREMENTS AND TIMING

Complete studies consisted of the determination of peak airway pressure; PA, LA, and femoral artery (FA) pressures; cardiac output and LLL PA flow; and blood gases and pH in the PA, LPV, and FA. Oxygen content was calculated using the P_{50} and the nomogram of Rossing and Cain (1966). The standard shunt formula was used to calculate shunt fraction. Baseline measurements were performed in all animals before insertion and after removal of the LLL, and any blood volume or blood gas abnormalities were corrected. Complete studies were performed 5, 20, 40, and 60 minutes after reimplantation of the lung. After that time, the LLL was ventilated with oxygen to

measure the shunt. Then, with the LLL disconnected, the right lung was ventilated with 100% oxygen to study its shunt fraction.

CONTROL AND ISCHAEMIA STUDIES

Group C (control) consisted of six dogs in which the entire protocol was carried out but the LLL was reimplanted immediately after being removed and weighed. Group WA (warm atelectatic) consisted of six dogs whose LLL were preserved in the atelectatic state at 38°C for three hours. Group WI (warm inflated) consisted of six dogs whose LLL were preserved for three hours at 38°C after being fully inflated with room air. Group WV (warm ventilated) consisted of seven dogs whose LLL were preserved for three hours at 38°C and ventilated with room air warmed to 38°C. Group CA (cold atelectatic) consisted of six dogs whose LLL were preserved for three hours at 6°C in the collapsed state. Group VCF (ventilated, cold, flushed) consisted of six dogs whose LLL were flushed with 100 ml of cold Collins solution (C2), then ventilated with room air at 6°C for 24 hours.

POST-MORTEM STUDIES

Dogs were killed with an overdose of barbiturate after a two-hour period of reimplantation, and the weights of the LLL and right lungs were determined. Samples for histological examination were obtained from the highest and most dependent zones.

Results (see tables 1–3)

BLOOD FLOW TO THE LEFT LOWER LOBE

Five minutes after reimplantation lungs stored in the warm atelectatic state had a considerably diminished blood flow (4%) as compared to the controls and the other groups. VCF lobes had significantly greater blood flow than WI and WV lobes. Similar results were obtained at 60 minutes except that group WI was no longer significantly different from group WA, and VCF lobes no longer had more blood flow that WI or WV lobes.

PULMONARY VASCULAR RESISTANCE

All groups except for VCF and WV had significantly greater pulmonary vascular resistance than controls. The VCF appeared to be completely protected from the considerable increase in resistance occurring in the other groups.

WEIGHT GAIN

All left lower lobes gained more than 50% of their original weight, but the WA group gained significantly more than the others. There was no

Table 1 *Statistical comparison of preservation techniques as indicated by* P *values*

		WA	*WI*	*WV*	*CA*	*VCF*
Blood flow (as percent cardiac output)						
5 Minutes						
Control	15·1± 4·5	<0·0001	NS	NS	NS	NS
WA	4·0± 1·7	—	<0·0005	<0·001	<0·0001	<0·0001
WI	11·6± 4·8	—	—	NS	NS	<0·05
WV	10·7± 5·0	—	—	—	NS	<0·01
CA	17·0± 7·9	—	—	—	—	NS
VCF	18·3± 4·8	—	—	—	—	—
60 Minutes						
Control	18·1± 5·1	<0·005	NS	NS	NS	NS
WA	8·4± 5·8	—	NS	<0·005	<0·05	<0·0005
WI	16·0± 8·2	—	—	NS	NS	NS
WV	21·3± 9·6	—	—	—	NS	NS
CA	20·0±11·2	—	—	—	—	NS
VCF	19·7± 5·3	—	—	—	—	—
Vascular resistance (mmHg g^{-1} min^{-1} ml^{-1})						
5 Minutes						
Control	1·2±0·5	<0·005	<0·05	NS	<0·001	NS
WA	9·6±4·4	—	<0·0005	<0·005	<0·0001	<0·0001
WI	4·7±1·7	—	—	NS	NS	<0·0001
WV	2·7±2·1	—	—	—	NS	NS
CA	3·1±1·2	—	—	—	—	<0·001
VCF	1·3±0·4	—	—	—	—	—
60 Minutes						
Control	1·0±0·27	<0·005	<0·05	NS	<0·05	NS
WA	5·0±2·5	—	<0·01	<0·001	<0·05	<0·0005
WI	4·1±1·1	—	—	NS	NS	<0·0001
WV	1·4±1·0	—	—	—	NS	NS
CA	2·4±1·4	—	—	—	—	<0·01
VCF	1·2±0·37	—	—	—	—	—

WA = Warm atelectatic; WI = Warm inflated; WV = Warm ventilated; CA = Cold atelectatic; VCF = Ventilated cold flushed.

Table 2 *Statistical comparison of preservation techniques as indicated by* P *values*

		WA	*WI*	*WV*	*CA*	*VCF*
% Weight gain						
Control	56± 40	<0·001	NS	NS	NS	NS
WA	231± 94	—	<0·05	<0·005	<0·05	<0·001
WI	131± 62	—	—	NS	NS	NS
WV	94± 50	—	—	—	NS	NS
CA	80±134	—	—	—	—	NS
VCF	69± 71	—	—	—	—	—
% Shunt						
Control	7·2±3·2	NS	NS	NS	NS	NS
WA	11·7±3·9	—	<0·01	<0·0005	<0·01	<0·001
WI	7·0±2·3	—	—	NS	NS	NS
WV	5·5±2·1	—	—	—	NS	NS
CA	6·5±2·6	—	—	—	—	NS
VCF	6·1±2·1	—	—	—	—	—

WA = Warm atelectatic; WI = Warm inflated; WV = Warm ventilated; CA = Cold atelectatic; VCF = Ventilated cold flushed.

Table 3 *Statistical comparison of preservation techniques as indicated by* P *values*

		WA	*WI*	*WV*	*CA*	*VCF*
Peak airway pressure (mm H_2O)						
5 Minutes						
Control	76·0±34·0	<0·05	NS	NS	NS	NS
WA	142·0±49·0	—	NS	NS	<0·05	<0·005
WI	100·0±47·0	—	—	NS	NS	NS
WV	97·0±33·0	—	—	—	NS	NS
CA	87·1±23·0	—	—	—	—	NS
VCF	67·0±28·0	—	—	—	—	—
60 Minutes						
Control	76·0±21·0	<0·005	NS	NS	NS	NS
WA	178·0±67·0	—	NS	<0·01	<0·0001	<0·0005
WI	102·0±65·0	—	—	NS	NS	NS
WV	91·0±42·0	—	—	—	NS	NS
CA	53·0±24·0	—	—	—	—	NS
VCF	74·0±19·0	—	—	—	—	—
$\dot{V}/\dot{Q}$ Ratio						
5 Minutes						
Control	1·6 ±0·3	<0·0005	<0·005	<0·0001	<0·05	NS
WA	7·7 ±4·1	—	NS	NS	NS	<0·001
WI	6·0 ±5·2	—	—	NS	NS	NS
WV	6·3 ±4·0	—	—	—	NS	<0·01
CA	4·9 ±2·0	—	—	—	—	<0·001
VCF	1·9 ±0·4	—	—	—	—	—
60 Minutes						
Control	1·37±0·25	<0·0001	<0·005	<0·01	<0·005	NS
WA	6·39±2·8	—	NS	<0·05	NS	<0·0001
WI	4·5 ±2·5	—	—	NS	NS	<0·01
WV	3·8 ±1·5	—	—	—	NS	<0·001
CA	4·6 ±3·0	—	—	—	—	<0·01
VCF	1·7 ±0·37	—	—	—	—	—

WA = Warm atelectatic; WI = Warm inflated; WV = Warm ventilated; CA = Cold atelectatic; VCF = Ventilated cold flushed.

correlation between weight gain and blood flow or vascular resistance within individual lobes. There was no significant difference in weight gain between groups WI, WV, CA, and VCF.

SHUNT FRACTION

Group WA had a significantly higher shunt fraction than all the other groups.

PEAK AIRWAY PRESSURE

Lungs stored in the warm atelectatic state were the only ones to develop higher airway pressure than controls.

V/Q RATIO

All groups developed significantly higher V/Q ratios than controls, except for group VCF, which was completely protected from this alteration.

HISTOLOGY (see figs 1 and 2)

All preserved lobes developed varying degrees of vascular congestion, peribronchial and perivascular

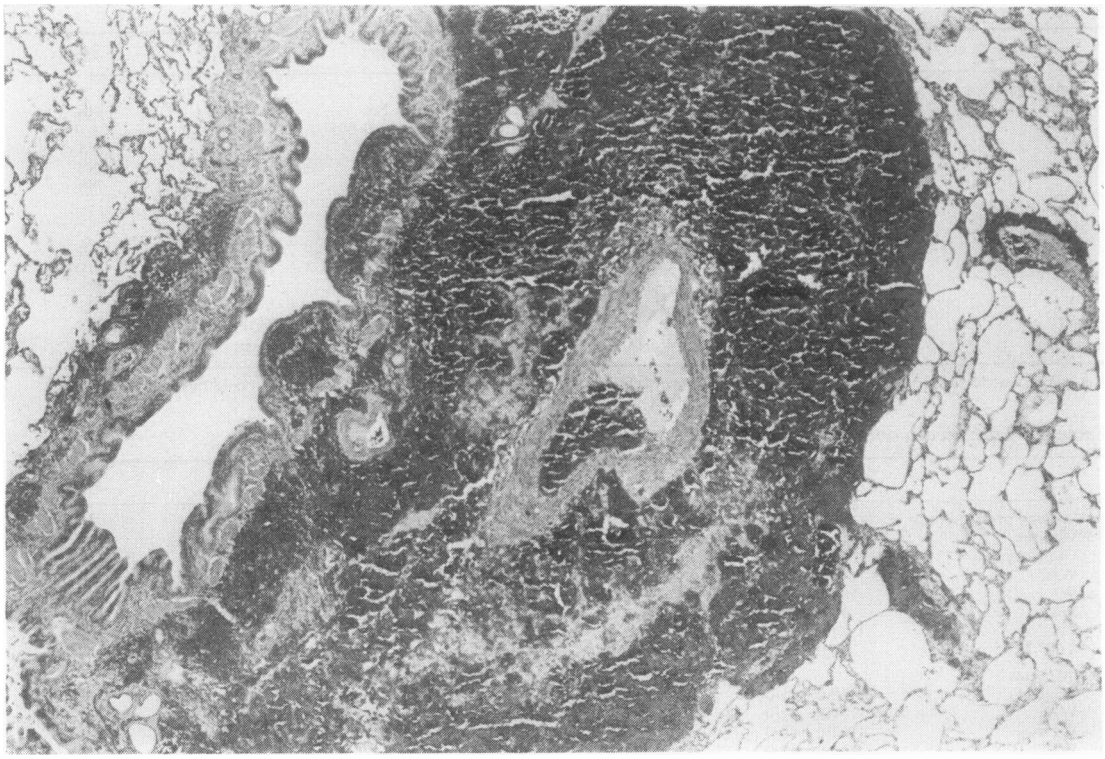

Fig 1 *Massive perivascular haemorrhage in dependent zone of lobe stored in warm atelectatic state. Note absence of pulmonary oedema.*

haemorrhage and oedema, and interstitial oedema. Intra-alveolar oedema was absent or minimal. Haemorrhage was more severe in the dependent than the upper zones, which often showed only peribronchial and perivascular oedema. There was no correlation between the degree of histopathological damage and haemodynamic measurements or weight gain.

Discussion

It has been repeatedly shown that the canine lung stored in the warm atelectatic state for three to six hours sustains an ischaemic injury that results in pulmonary oedema soon after reimplantation and early death (Borrie and Lichter, 1964; Homatas *et al,* 1968; Stevens *et al,* 1969; Veith *et al,* 1971; Fonkalsrud *et al,* 1974; Kondo *et al,* 1974). When the animal must rely entirely on the reimplanted lung for oxygenation the time limit of warm ischaemia is 30 minutes in the atelectatic state (on one reimplanted lung) and one to three hours in the inflated state (with bilateral reimplantation) (Veith *et al,* 1971; Kondo *et al,* 1974).

Although technique and results vary greatly, it would appear that ventilation, and probably inflation, increase the tolerance of the lung to warm ischaemia (Stevens *et al,* 1969; Joseph and Morton, 1971; Veith *et al,* 1971; Fonkalsrud *et al,* 1975). Hypothermia in combination with initial flushing and ventilation, or hyperbaric oxygenation, however, appear to offer the most effective methods of lung preservation. There are several reports of successful 24-hour preservation as determined by function studies or ability to support life (Blumenstock *et al,* 1965; Largiader *et al,* 1965; Garzon *et al,* 1968; Thomas and Buchman, 1971; Veith *et al,* 1971; Castagna *et al,* 1972; Grosjean *et al,* 1972; Crane *et al,* 1975).

Most of this information has been derived from studies of animal survival, and little attention has been directed towards the immediate post-preservation period. It seems likely, however, that specific changes in pulmonary function occur during and soon after preservation, and that these

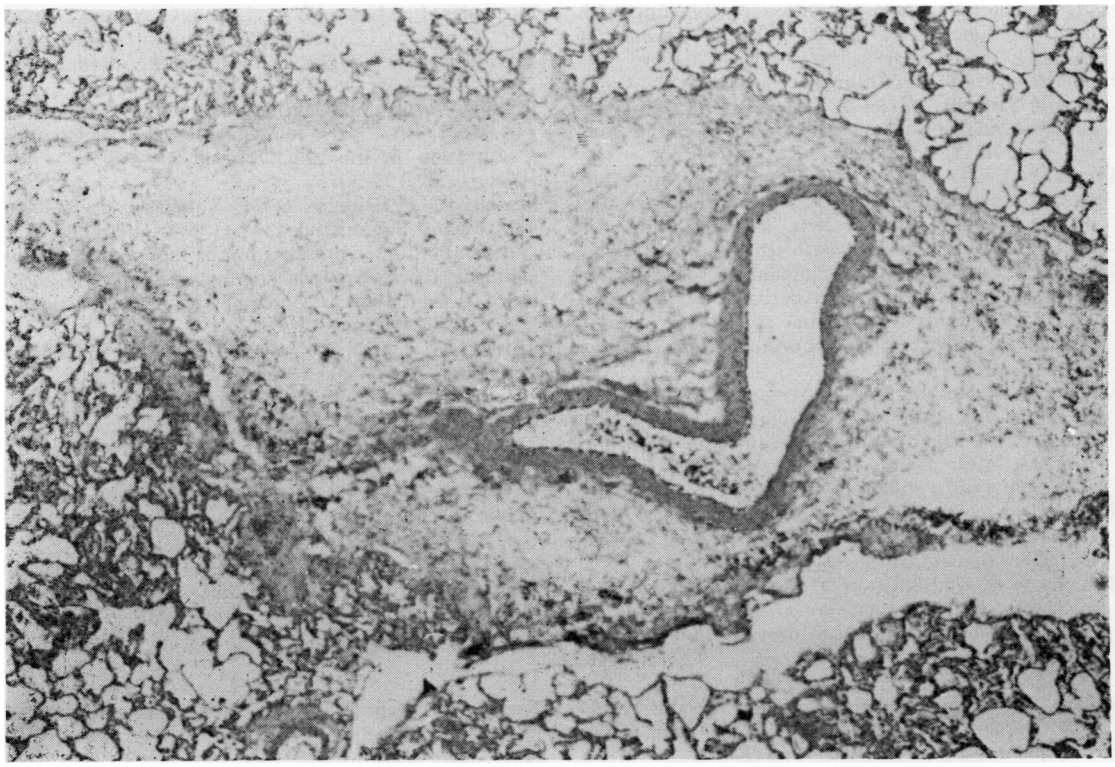

Fig 2 *Massive perivascular oedema in non-dependent zone of same lobe. Note absence of haemorrhage.*

changes may predict ultimate survival and function. Our experiments were designed to define these changes and to correlate them with survival data previously reported.

Our results clearly indicate the superiority of hypothermia, inflation, flushing with Collins solution, and ventilation over warm atelectatic lung preservation. Blood flow, vascular resistance, shunt fraction, and weight gain in the immediate post-preservation period were significantly better in these groups. The inability of our methods to separate the effects of ventilation, inflation, and hypothermia from each other and from controls probably relate to the relatively short preservation period. It is clear, however, that the combination of C2 flushing, ventilation, and hypothermia resulted in the best preservation. Although the reported differences between groups were statistically significant, there was considerable variability within each group. This is similar to reported survival data and may suggest that lungs may have variable sensitivity to ischaemia.

Combining these data with survival reports suggests that initial flow to the preserved lung, pulmonary vascular resistance, shunt fraction, weight gain, and airway pressure will be of value in predicting the ultimate outcome in any individual lung transplant. This information could be of potential clinical significance in that it might lead to a screening method for human lung homografts. Because of the observed variability however, a study is needed in which early performance is correlated with the survival and long-term function of each preserved lobe. Such a study is now in progress.

References

Blumenstock, D A, Lempert, N, and Morgado, F (1965). Preservation of the canine lung in vitro for 24 hours with the use of hypothermia and hyperbaric oxygen. *Journal of Thoracic and Cardiovascular Surgery*, **50**, 769–774.

Borrie, J, and Lichter, I (1964). Lung transplantation, technical problems. *Thorax*, **19**, 383–396.

Castagna, J T, Shors, E, and Benfield, J R (1972). The role of perfusion in lung preservation. *Journal of Thoracic and Cardiovascular Surgery*, **63**, 521–526.

Crane, R, Torres, M, Hagstrom, J W, Koerner, S K, and Veith, F J (1975). Twenty-four hour

preservation and transplantation of the lung without functional impairment. *Surgical Forum*, **26**, 111–113.

Fonkalsrud, E W, Higashijima, I, Sarwat, A K, Arima, E, and Sanchez, M (1974). Evaluation of pulmonary function in the ischemic nonventilated canine lung. *Surgery*, **76**, 527–532.

Fonkalsrud, E W, Sanchez, M, Lasaletta, L, Smeesters, C, and Higashijima, I (1975). Extended preservation of the ischemic canine lung by ventilation with PEEP. *Journal of Surgical Research*, **18**, 437–445.

Garzon, A A, Cheng, C, Pangan, J, and Karlson, K E (1968). Hypothermic hyperbaric lung preservation for twenty-four hours with replantation. *Journal of Thoracic and Cardiovascular Surgery*, **55**, 546–554.

Grosjean, O, Noirclerc, M, Duvinage, J F, Sudan, N, Tedeschi, J, Coutant, P, and Lejeune, G (1972). Pulmonary transplantation with immediate return of function after twenty-four hours of preservation. *Acta Chirurgica Belgica*, **71**, 321–333.

Homatas, J, Bryant, L, and Eiseman, B (1968). Time limits of cadaver lung viability. *Journal of Thoracic and Cardiovascular Surgery*, **56**, 132–140.

Joseph, W L, and Morton, D L (1971). Influence of ischemia and hypothermia on the ability of the transplanted primate lung to provide immediate and total respiratory support. *Journal of Thoracic and Cardiovascular Surgery*, **62**, 752–761.

Kondo, Y, Turner, M D, Cockrell, J V, and Hardy, J D (1974). Ischemic tolerance of the canine autotransplanted lung. *Surgery*, **76**, 447–453.

Largiader, F, Manax, W G, Lyons, G W, and Lillehei, R C (1965). Experimentelle homotransplantation konservierter lungen. *Schweizerische Medizinische Wochenschrift*, **95**, 1151–1154.

Rossing, R C, and Cain, S M (1966). A nomogram relating Po_2, pH, temperature and hemoglobin saturation in the dog. *Journal of Applied Physiology*, **21**, 195–201.

Stevens, G H, Rangel, D M, Yakeishe, Y, Sanchez, M D, and Fonkalsrud, E W (1969). The relationship of ventilation to preservation of the ischemic canine lung graft. In *Current Topics in Surgical Research*, vol 1, edited by G Zuidema, pp 51–56. Academic Press, New York.

Taft, P M, Collins, G M, Grotke, G T, and Halasz, N A (1976). Warm ischemic injury of the lung. *Journal of Thoracic and Cardiovascular Surgery*, **72**, 784–787.

Thomas, P A, and Buchman, R J (1971). Successful 20-hour preservation of ischemic canine lung by hypothermia combined with minimal ventilation. *Journal of Thoracic and Cardiovascular Surgery*, **62**, 176–182.

Veith, F J, Sinha, S B, Graves, J S, Boley, S J, and Dougherty, J C (1971). Ischemic tolerance of the lung. *Journal of Thoracic and Cardiovascular Surgery*, **61**, 804–810.

Requests for reprints to: Dr N A Halasz, Department of Surgery, University Hospital, 225 Dickinson Street, San Diego, California 92103, USA.